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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte MICHAEL ROSENBLUM and LAURA K. SHAWVER

Appeal 2008-2931
Application 09/320,156
Technology Center 1600

Decided: July 31, 2008

Before DEMETRA J. MILLS, LORA M. GREEN, and
FRANCISCO C. PRATS, *Administrative Patent Judges*.

GREEN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is a decision on appeal[1] under 35 U.S.C. § 134 from the Examiner's final rejection of claims 15-17 and 19. We have jurisdiction under 35 U.S.C. § 6(b). Claims 15 and 17 are representative of the claims on appeal, and reads as follows:

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[1] This Appeal was heard on July 8, 2008.

15. A composition comprising a conjugate of tumor necrosis factor to a single chain antibody exhibiting binding specificity for an extracellular epitope of c-erbB-2 protein, wherein said single chain antibody is scFv-23.

17. The composition of Claim 15, wherein said conjugate is recombinantly produced by fusing a gene encoding said single chain antibody to a gene encoding tumor necrosis factor.

The Examiner relies on the following references:

King	US 5,587,458	Dec, 24, 1996
Gillies	US 5,650,150	Jul. 22, 1997

Rosenblum, "Antibody-Medicated Delivery of Tumor Necrosis Factor (TNF-α): Improvement of Cytotoxicity and Reduction of Cellular Resistance," *Cancer Communications*, Vol. 3, No. 1, pp. 21-27 (1991).

We affirm.

BACKGROUND

According to the Specification:

> The present invention provides a composition comprising a conjugate of a cellular targeting moiety, *e.g.*, an antigen binding region, exhibiting binding specificity for the c-erbB-2 protein and a cell growth modulator, *e.g.*, a toxin or growth suppressing reagent. This composition acts as an immunotoxin to specifically target a cell growth modulator to tumor cells overexpressing the c-erbB-2 protein. . . . The cytotoxic moiety may be a toxin, a cytocidal drug, a cytostatic drug, or a biological response modifier.

(Spec. 3-4).

As to biological response modifiers, the Specification teaches:

> Biological response modifiers which may be coupled to the TAb 250 antibody and used in the present invention include, but are not limited to, lymphokines and cytokines such as IL-1,

> IL-2, interferons . . ., TNF, LT, TGF-β, and IL-6. These biological response modifiers have a variety of effects on tumor cells. Among these effects are increased tumor cell killing by direct action as well as increased tumor cell killing by increased host defense mediated processes. Conjugation of antibody TAb 250 to these biological response modifiers will allow selective localization or targeting to tumors or cells overexpressing c-erbB-2 and, hence, improved antiproliferative effects. Non-specific effects leading to toxicity of non-target cells will be minimized since the selected cell growth mediator is ineffective absent a targeting component.

(*Id.* at 43-44.) As to TNF in particular, the Specification teaches, citing Rosenblum, that previous studies "have demonstrated that chemical conjugates of human tumor necrosis factor (TNF) and monoclonal antibodies display significant targeted cytotoxic properties against tumor cells in culture which appears to be far superior to those of native TNF." (*Id.* at 93.)

The Specification teaches further:

> In another embodiment of the instant invention, there is provided a conjugate of tumor necrosis factor to an antibody exhibiting binding specificity for an extracellular epitope of c-erbB-2 protein. The antibody may be an intact full length antibody with either the heavy chain or light chain peptide conjugated to tumor necrosis factor. Alternatively, the antibody may be or a Fv fragment with the toxin linked to either the V_L, or V_H, peptide. In the preferred embodiment, conjugate is a fusion protein between a single chain antibody and tumor necrosis factor which is preferably produced by recombinantly fusing a gene encoding a single chain antibody to a gene encoding tumor necrosis factor. One possible sFv is scFv-23.

(*Id.* at 5-6.)

The Specification further defines "immunoglobulin" or "antibody peptide(s)" as referring to "an entire immunoglobulin or antibody or any functional binding fragment of an immunoglobulin molecule. Examples of such peptides include complete antibody molecules, antibody fragments, such as Fab, $F(ab')_2$, CDRs, V_L, V_H, and any other portion of an antibody, particularly those exhibiting antigen binding specificity or affinity." (*Id.* at 17-18.) "An 'Fab' fragment comprises a light chain and the N-terminal portion of the heavy chain which are linked together by disulfide bonds. It typically has a molecular weight of approximately 50 kD and contains a single antigen binding site. Fab fragments may be obtained from $F(ab')_2$ fragments by limited reduction, or from whole antibody by digestion with papain in the presence of reducing agents." (*Id.* at 21.)

Figure 9 shows "the configuration and sequence of the scFv-gelonin immunotoxin." (*Id.* at 7, ll. 19-21.) The antibody fragment was cloned using the 212 linker, which is a 12 amino acid linker (*id.* at 71.) The Specification teaches further that a "person having ordinary skill in this art would readily recognize that certain modifications in the sequence of scFv-23 could be made, e.g., a VH - Linker - VL format and CDR grafting to construct a humanized or chimeric antibody to minimize potential immunogenicity problems with this murine antibody." (*Id.* at 72.)

Figure 25 is a schematic showing the design of the sFv23/TNF fusion construct (*id.* at 15, ll. 8-10). That construct has a flexible 14 amino acid linker (*id.* at 94).

DISCUSSION

Claims 15 and 19 stand rejected under 35 U.S.C. § 103(a) as being obvious over the combination of King and Rosenblum.

King is cited for teaching "conjugates of the single chain antibody, e23 (column 6, lines 58-62), which appears to be identical to the instant scF23." (Ans. 3.) King is cited further for teaching "conjugation of anti-ERbB2 antibodies with anti-tumor drugs, toxins or radionuclide (column 4, lines 9-15)." (*Id.*) The Examiner acknowledges that King does not "specifically teach conjugation of e23 to TNF." (*Id.*)

Rosenblum is cited for teaching "that the sensitivity of tumor cells to TNF was dramatically augmented by antibody-mediated delivery to said cells." (*Id.*)

The Examiner concludes that it "would have been prima facie obvious . . . to substitute TNF for the cytotoxic moiety in the e23 conjugates taught by King." (*Id.*) According to the Examiner, "[o]ne of skill in the art would have been motivated to do so by the teachings of Rosenblum [ ] pointing out the benefit of antibody-mediated delivery of TNF to tumor cells relative to the administration of free TNF." (*Id.*)

The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) secondary considerations of nonobviousness, if any. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). The Supreme Court has recently emphasized that "the [obviousness] analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and

creative steps that a person of ordinary skill in the art would employ." *KSR Int'l v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007). "The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *Id.* at 1739. Moreover, an "[e]xpress suggestion to substitute one equivalent for another need not be present to render such substitution obvious." *In re Fout*, 675 F.2d 297, 301 (CCPA 1982). We conclude that the Examiner has set forth a prima facie case of obviousness. We thus turn to Appellants' arguments in rebuttal.

Appellants argue that King relates to a different single chain antibody, as the scFv construct referred to in the claims is the one shown in Figure 25 (Reply. Br. 2).[2] Specifically, Appellants argue that King refers to a different single chain antibody as the King e23 scFv construct incorporates a 14 amino acid linker, whereas the construct of Appellants' contains a different linker of 12 amino acids (*id.*).

Appellants' argument is not convincing. First, Appellants' Specification refers to the construct of both Figure 9 (which has a 12 amino acid linker) and Figure 25 (which has a 14 amino acid linker) as incorporating scFv-23. Moreover, the Specification teaches that the ordinary artisan would recognize that modifications may be made (Spec. 72). Thus, there is nothing in the Specification that limits the single chain antibody, scFv-23, to the sequence and construct shown in either Figures 9 or 25 of the instant Specification.

[2] The Reply Brief references the construct of Figure 9, but at oral argument Appellants stated that reference is incorrect, and the Reply Brief should have referred to Figure 25.

Appellants argue that there is no motivation to combine King and Rosenblum (App. Br. 3). King, Appellants assert, does not mention conjugation to TNF, or any cytokine, and thus provides no motivation to employ TNF (*id.*). Appellants argue further that King only teaches inhibitors of protein synthesis, and thus "cannot be said to suggest proteins that are not inhibitors of protein synthesis." (Reply Br. 3.) According to Appellants, King

> provides no motivation or suggestion to combine with another reference, and certainly not Rosenblum, because King heralds the use of conjugation of the antibody e23 to the exemplary *pseudomonas* exotoxin A variant PE40 and derivative thereof as cytotoxic moieties . . . so there would be no motivation to utilize any reagents other than what is taught by King as being successful or as alternatives thereto. Given that King reports success with the technology, one of skill in the art would find no motivation to expend time and resources to alter successful protocols.

(App. Br. 4.)

Appellants argue further that there is no motivation to combine Rosenblum with King, as Rosenblum also "reports success with his technology." (*Id.* at 5.) Moreover, Appellants assert, "King was filed two years after Rosenblum, and yet King chose not to describe or even suggest conjugating scFv23 to TNF even though a variety of cytotoxic moieties were listed in King." (*Id.*)

First, as to motivation to combine, the Supreme Court in *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1739 (2007), rejected a rigid application of the teaching-suggestion-motivation test. The Court recognized that it is often necessary to look at the interrelated teaches of multiple references; the effects of demands of the marketplace; and the background knowledge

possessed by a person of ordinary skill, "all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed." *Id.* at 1740-41. Moreover, the "obviousness analysis cannot be confined by a formalistic conception of the words teaching, suggestion, or motivation, or by overemphasis on then importance of published articles and explicit content of issued patents." *Id.* at 1741. Finally, one "of the ways in which a patent's subject matter can be proved obvious is by noting that there existed at the time of the invention a known problem for which there was an obvious solution encompassed by the patent's claims." *Id.* at 1742.

Second, if we were to accept Appellants arguments at face value, it would obviate § 103 of the patent statute. The fact that both King and Rosenblum report success with their methods does not mean that neither reference can then be used in an obviousness rejection. Similarly, the fact that King was filed two years after Rosenblum is irrelevant to the obviousness analysis, because if we were to follow Appellants argument to the logical end, there could never be an obviousness rejection based on references that were not published on the same date.

Moreover, we recognize that an invention "composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR*, 127 S. Ct. at 1741. "Often, it will be necessary . . . to look to interrelated teachings of multiple [references] . . . and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed[.]" *Id.* at 1740-41. "[T]his analysis should be made explicit" (*id.* at 1741), and it "can be important to identify a reason that would have

prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does" (*id.*).

In this case, King teaches conjugates of the single chain antibody, e23, which, as noted by the Examiner, appears to be identical to the instant scFv-23 (Ans. 3). King specifically discloses the e23 antibody and single chain antibodies derived therefrom (col. 6 ll. 49-62). King also teaches the use of monoclonal or single chain antibodies which specifically bind to an extracellular domain of the cerbB-2 protein (King, col. 3 ll. 47-51), which may be administered as a conjugate to a cytotoxic moiety, such as an anti-tumor drug, toxin, or radionuclide (col. 4 ll. 13-15). Specifically, King teaches that the antibodies may be attached to cytotoxic materials, including radioactive materials, anti-cancer drugs, inhibitors of protein synthesis, and agents that bind DNA (col. 8, ll. 47-54).

Rosenblum teaches a conjugate of recombinant TNFalpha to an antibody that recognizes an antigen present on 80% of melanoma cells (Rosenblum, abstract). Rosenblum teaches further that "[b]ecause of their unique abilities to localize within human tumors after systemic administration, antibodies have the potential to serve as targeting vehicles for specific delivery of cytotoxic chemotherapeutic agents, toxic peptides, biological response modifiers, and therapeutic radionuclides." (*Id.* at 21, paragraph bridging first and second columns.) According to Rosenblum, TNFalpha is cytotoxic to a number of mammalian and humor tumor cells (*id.* at second column), and that "the sensitivity of cells to TNF was dramatically augmented by specific antibody mediated delivery to tumor cells" (*id.* at Abstract).

Thus, it would have been obvious to the ordinary artisan at the time the invention to use the TNF as the cytotoxic moiety in the e23 single chain conjugate of King because King teaches conjugation to cytotoxic moieties and Rosenblum teaches that the sensitivity of cells to TNF was dramatically augmented by specific antibody mediated delivery to tumor cells. The ordinary artisan would understand that the monoclonal of Rosenblum and the single chain antibody of King both allow for targeting of tumor cells. Although King exemplifies the use of *Pseudomonas* exotoxin A variant PE40, King teaches the use of cytotoxic moieties generally, and to those of ordinary skill in an art, it is generally obvious to alter a known product by substituting a known equivalent for one of its components. *See, e.g., Hotchkiss v. Greenwood*, 52 U.S. 248 (1850) (substitution of porcelain door knob in known process of making metal or wood door knobs held obvious); *In re Mayne*, 104 F.3d 1339, 1340 (Fed. Cir. 1997) ("Because the applicants merely substituted one element known in the art for a known equivalent, this court affirms [the rejection for obviousness]."); *Richardson-Vicks Inc. v. Upjohn Co.,* 122 F.3d 1476, 1483-1484 (Fed. Cir. 1997) (The combination of ibuprofen and pseudoephedrine in a single dosage was "clearly suggested by the prior art including CO-TYLENOL®, which combined an analgesic with **pseudoephedrine** into a single tablet"; "[i]buprofen was a known analgesic that was interchangeable with either **aspirin** or **acetaminophen**.").

Appellants argue further that Rosenblum teaches away from using a single chain antibody, and at best, only suggests conjugating TNF to another monoclonal antibody specific for melanoma cells (App. Br. 5). Moreover, according to Appellants, there is no guidance in King as to "which of the

plethora of antibodies in the art to select from." (*Id.*) Thus, Appellants assert, the Examiner has engaged in improper hindsight reconstruction (*id.*).

"Under the proper legal standard, a reference will teach away when it suggests that the developments flowing from its disclosures are unlikely to produce the objective of applicant's invention. A statement that a particular combination is not a preferred embodiment does not teach away absent clear discouragement of that combination." *Syntex (USA) LLC v. Apotex, Inc.*, 407 F.3d 1371, 1380 (Fed. Cir. 2005) (citations deleted).

As already noted, Rosenblum teaches that "[b]ecause of their unique abilities to localize within human tumors after systemic administration, antibodies have the potential to serve as targeting vehicles for specific delivery of cytotoxic chemotherapeutic agents, toxic peptides, biological response modifiers, and therapeutic radionuclides." (*Id.* at 21, paragraph bridging first and second columns.) The ordinary artisan would understand that the ability of an antibody to localize within human tumors would be shared by both the intact antibody and a single chain fragment thereof, as each contains an antigen binding regions (*see, e.g.*, King, col. 3 ll. 47-51 (teaching the use of both monoclonal or single chain antibodies which specifically bind to an extracellular domain of the cerbB-2 protein); *see also* Spec. 5-6 (noting that the antibody may be an intact full length antibody with either the heavy chain or light chain peptide conjugated to tumor necrosis factor, or maybe a Fv fragment with the toxin linked to either the V_L, or V_H, peptide)).

Thus, we conclude that the Examiner has set forth a prima facie case of obviousness that has not been adequately rebutted by Appellants, and the rejection is affirmed.

Claims 15-17 and 19 stand rejected under 35 U.S.C. § 103(a) as being obvious over the combination of King and Rosenblum as further combined with Gillies.

King and Rosenblum are relied upon as above (Ans. 3-4). The Examiner acknowledges that the combination "does not teach the recombinant fusion of TNF to e23." (*Id.* at 4.)

Gillies is relied upon for teaching "the recombinant fusion of TNF-alpha to the heavy chain variable region of an antibody," and for teaching "that the recombinant method is superior to the chemical conjugation because it avoids the unexpected consequences associated with chemical coupling." (*Id.*)

The Examiner concludes that it would have been obvious "to fuse TNFalpha to the e23 antibody in lieu of chemical conjugation" because Gillies teaches it avoids the unexpected consequences associated with chemical coupling (*id.*).

As to claims 15 and 19, Appellants reiterate their arguments as to the combination of King and Rosenblum (App. Br. 7). We therefore affirm the rejection as to claims 15 and 19 for the reasons set forth above as to the combination of King and Rosenblum.

Appellants argue further that Gillies only discloses fusion proteins of cytokines, such as TNF, to full length antibodies, wherein the cytokine is attached to the heavy chain of the antibody (Reply Br. 5). Single chain antibodies, Appellants assert, do not have a heavy chain (*id.*). Appellants also argue that Gillies teaches that combining an antibody to a cytokine is "inherently unpredictable," as ***"the fusion of protein domains to the carboxy-termini of immunoglobulin chains or fragments can have***

***unexpected consequences for the activities of both the protein to be fused and the immunoglobulin, particularly as far as antigen binding, assembly and effector functions are concerned.*"** (Reply Br. 5 (quoting Gillies, col. 1, ll. 41-50).) Thus, Appellants assert, both "Rosenblum and Gillies point us away from using a single-chain antibody to deliver TNF." (Reply Br. 6.)

Appellants' argument is not convincing. King teaches the use of recombinant antibodies (col. 7 ll. 21-24), and teaches further that methods "for making recombinant antibodies by recombinant antibodies are well known in the art" (*id.* at 7 ll. 41-42). King also exemplifies a single chain antibody immunotoxin, in which a single chain of the e23 antibody is fused to a Pseudomonas exotoxin A variant, PE40 (col. 18, Example 10). Specifically, the light chain of e23, a 14 amino acid linker, and the variable region of the heavy chain of e23 was fused to PE40 (col. 19, ll. 10-25).

Gillies teaches immunoconjugates of a cytokine such as TNFalpha to an antibody (Abstract). Although Gillies teaches that a preferred embodiment the cytokine is linked to the constant region of the heavy chain of the antibody (col. 2, ll. 31-35; *see also* Figure 1), as King teaches conjugation of a cytotoxic moiety to the claimed single chain antibody e23 (scFv23), the ordinary artisan would have understood that another cytotoxic moiety, such as the TNFalpha taught by Gillies, could have been attached to the single chain antibody of King by recombinant methods in the same way.

Moreover, as to Appellants' argument that combining an antibody to a cytokine is "inherently unpredictable," because King teaches combining a single chain antibody to a cytotoxic moiety, King provides a reasonable expectation of success of arriving at the claimed invention. *See In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988) (noting that all that is required

is a reasonable expectation of success, not absolute predictability of success).

As to claims 16 and 17, Appellants argue:

> Gillies concerns recombination of TNF with a heavy chain variable region of an antibody. Having an earlier filing date than King and Rosenblum, the skilled artisan would be aware of Gillies' techniques to employ recombinant fusions, and yet neither King nor Rosenblum chose to utilize such methods in their working Examples. Therefore, one of skill in the art would similarly not be motivated to employ recombination fusions over the preferred conjugation techniques of King and Rosenblum.

(App. Br. 8.)

Again, Appellants arguments are not convincing, because as noted above, if we were to exclude references that have an earlier publication date than another reference being used in the obviousness analysis, we would eviscerate section 103 of the patent code. Moreover, as already noted, King specifically teaches production of a conjugate of a cytotoxic moiety (PE40) to a e23 (svF23) single chain antibody by recombinant means. The ordinary artisan would understand that the same methods could be used to produce other conjugates of an e23 (svF23) single chain antibody to a cytotoxic moiety, such as the TNF alpha taught by Rosenblum and Gillies.

Thus, we again conclude that the Examiner has set forth a prima facie case of obviousness that has not been adequately rebutted by Appellants, and the rejection is affirmed.

CONCLUSION

In summary, we find that the Examiner has set forth a prima facie case of obviousness that has not been adequately rebutted by Appellants. Thus, we affirm the rejection of claims 15 and 19 under 35 U.S.C. § 103(a) as being obvious over the combination of King and Rosenblum, and also affirm the rejection of claims 15-17 and 19 under 35 U.S.C. § 103(a) as being obvious over the combination of King and Rosenblum as further combined with Gillies.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

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